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ABSTRACT

Reported were results of the first year of a 3-year physiological study of the hyperkinetic child. The male subjects were 6 to 9 years of age, attending school, without sensory defects, 80 or above in Wechsler Intelligence Scale for Children Full Scale, off medication for 3 months prior to testing, and diagnosed as hyperactive. Electroencephalograph and evoked cortical measures were made for 31 hyperkinetic children and 21 normal controls in order to predict clinical response to stimulant medication. Experimental design included a structured interview, teacher and parent rating scales, medical evaluation, psychological testing, watching a video taped cartoon while taking cortical measures at beginning and end of 3-week period, and Ritalin and placebo treatments. Overall results indicated existence of a fundamental physiological difference between children responding well and poorly to stimulant medication. Low central nervous system arousal and good clinical response to stimulant treatment were found to characterize one group, while high central nervous system arousal and poor response to stimulant treatment were found to typify the other group. (CB)

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NEUROLOGICAL STUDIES OF THE HYPERKINETIC CHILD I

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[illegible] THE HYPERKINETIC CHILD I

[illegible] Hyperkinetic Child Syndrome, first described over 100 years ago,(1) has been redefined over the years by a number of studies(2,3,4,5). They indicate a syndrome that begins early in life, is more common in boys, and is characterized by a symptom pattern of overactivity, distractibility, impulsivity, and excitability. Hyperactive children have difficulties with peer relations; disciplinary and specific learning problems are common. The etiology of the syndrome is unknown, with theories ranging from psychogenic to organic, from disordered metabolism to inborn temperment.

This paper describes EEG and evoked cortical potential measures which predict clinical response to stimulant medication. These measures also suggest a model for understanding the neurophysiological process underlying the disordered behavior in the Hyperkinetic Child Syndrome.

The heterogeneity of diagnostic categories, a continuing problem in adult psychiatry,(6) presents a more substantial challenge in child psychiatry(7). Robins and Guze(8) describe a method for achieving diagnostic validity in psychiatric illness consisting of five phases: clinical description, laboratory studies, exclusion of other disorders, follow-up studies and family studies. To this scheme the present authors add a sixth phase: results of treatment. We feel that in the absence of known etiology or pathogenesis, as in the more common psychiatric disorders, marked differences in response to adequate trials of the same treatment, such as between complete recovery and chronic illness, should suggest that the group is not homogeneous. This paper illustrates how hyperactive children may be classified on the basis of response to treatment and illustrates the use of laboratory studies that attempt to validate this classification.

[illegible] hyperkinetic children and twenty-one normal controls were evaluated. The hyperkinetic children were referred to Gateways Hospital's hyperkinetic children's clinic for evaluation and treatment. To be included in this study, a hyperkinetic patient had to be: (1) male; (2) between the ages of six and nine years; (3) attending school; (4) without sensory defects; (5) 80 or above in IQ (WISC Full Scale); (6) off medication for a period of at least 3 months prior to testing; and (7) diagnosed as suffering from the hyperactive child syndrome by the criteria of Stewart et al.(9), which requires definite evidence of hyperactivity and distractibility and the presence of any 6 of the 28 symptoms found to be most characteristic of the syndrome.

A structured interview was obtained on all subjects which included: identification (19 items), history of present illness, behavior and symptom inventory (54 items), developmental history (13 items), past medical history (9 items), and family history (25 items). A teacher rating scale and a parent rating scale were obtained on all subjects. The rating scale for teachers consisted of thirty-six items of classroom behavior arranged in check list form so that the teacher could check off whether each individual item of behavior was exhibited by the child: (a) not at all; (b) just a little; (c) pretty much; and (d) very much. These individual items were given numerical scores of 0, 1, 2, and 3 respectively, and then summed to give a total rating score across all behavior items.

All hyperkinetic children were examined by a child psychiatrist and a pediatric neurologist. A clinical EEG was obtained on all experimental subjects. In addition, all subjects received a battery of psychological tests including the WISC, the WRAT, the ITPA, the Goodenough-Harris Draw-A-Person, the Bender-Gestalt, and the Lincoln Oseretsky.

[illegible] spectral analyses of the EEG, mean [illegible] range of amplitude of the EEG, auditory evoked cortical [illegible], skin conductance level (SCL), and measurement of EEG movement [illegible]. All laboratory and psychological tests were run on the hyper- [illegible] subjects before and after three weeks of drug treatment. The post- [illegible] laboratory studies were carried out approximately ninety minutes following a single oral dose of medication (Placebo or Ritalin).

Subjects were seated in an easy chair in a soundproof room and were asked to watch a video taped cartoon shown on a TV set throughout the experiment. The TV sound was adjusted to 50 d.b. sound pressure level. Auditory click stimuli of .1 msec duration with an intensity of 90 d.b. above auditory threshold level were presented at two rates: fast, (2 stimuli per second); and slow, (1 stimulus every 2.5 seconds). Blocks of clicks were presented with 16 slow stimuli alternating with 64 fast stimuli. Subjects were instructed to ignore the clicks. The EEG was recorded from double vertex electrodes located at 2.5 cm from the midline and referred to the earlobe of the respective side. A special average of the EEG in these two channels was obtained on-line and stored on digital tape. The EEG was sampled 100 msec before and 300 msec after each click stimulus. Four- hundred individual evoked responses were obtained at the slow stimulus rate and 1600 individual click evoked responses were obtained at the fast rate. Also, 400 non-stimulus control EEG samples were stored on tape. The total experimental time was approximately 40 minutes.

The SCL was obtained as a d.c. resistance phenomenon through Beckman silver-silverchloride electrodes (diameter of 10 mm) coated with isotonic electrode paste applied to the first and third fingertip of the subject's

[illegible] recordings were obtained with a Grass Model 7 polygraph and [illegible] digital tape every 2 seconds. Processing of the digital tapes was [illegible] Sperry Univac 1108 digital computer. Amplitude histograms obtained from sampling EEG samples taken every 2 msec throughout the [illegible] experiment were computed off-line. The mean resting EEG amplitude and range of the mean resting EEG amplitudes were also computed. The power spectral analyses were computed for each of the 2400 1/2 second EEG samples (40 minutes), and an average power spectral analysis was computed for each subject.

A double blind methylphenidate-placebo treatment evaluation was obtained on thirty-one hyperkinetic children. Treatment was carried out for a three-week period. The dosage was adjusted upward at weekly intervals until a good clinical response was obtained or until side effect prohibited further increase. Teacher rating scales were obtained on all patients before and immediately after treatment. These scales were scored and response to treatment was judged on the basis of improvement or lack of improvement in these scores.

Results: The hyperkinetic children and the controls were well matched for age, but the normal control group had significantly ($p < .001$) higher IQ's (Figure 1). The two groups differed clinically on many of the structured interview items and most of these differences were still present when the groups were more closely matched for IQ (Table 1). The mean ages were 92.9 months for this smaller sample of 14 hyperkinetics, and 92.7 months for the controls. The mean IQ for this hyperkinetic group was 109.1 and 110.4 for the controls. Table 1 illustrates some of the differences between these well matched hyperkinetic children and the normal controls. The

[illegible] the normals at $p < .001$ on [illegible] clinical evaluation. The comparison of physiological laboratory measures between the normal controls and hyperkinetic children will be reported elsewhere. Based upon change scores in the teacher rating scale before and after treatment, the 14 patients on Ritalin showed significantly more improvement ($p < .001$) than did the 16 placebo patients.

The remainder of the results to be reported deals with the comparison between those patients with a good and those with a poor clinical response to Ritalin treatment. The six best responders to Ritalin were compared with the five worst responders (Figure 2). It can be seen that the two groups are similar in respect to age and IQ (Full Scale WISC). The best-response group had a mean improvement of 71 percent and the worst-response group had a mean improvement of 16 percent. This difference was significant at $p < .001$. The best-response group had higher before-treatment teacher rating scale scores (mean of 39) than the worst-response group (mean of 46). These differences were not statistically significant. A higher score on the teacher rating scale indicates more behavior pathology.

Eleven control subjects who were matched for age, sex, and IQ with the above 11 hyperkinetic children (6 best and 5 worst responders) were selected. These 11 controls were then compared with the best and worst patient responders on several before-treatment laboratory measures (Figure 3). It can be seen that, before treatment, the best response hyperkinetics and the worst-response hyperkinetics both tend to differ from normal controls, but in different directions. For example, skin conductance level in the best-response group is lower than normals, and in the worst-response group higher than normals. Also, mean resting EEG amplitude, resting EEG amplitude range,

[illegible] and normals were also higher than normal in the [illegible] group, and lower than the normals control in the worst-[illegible] group. Further, when the hyperkinetics with the best response to Ritalin were compared before treatment with those with the worst response, the latter group was found to have significantly higher resting EEG amplitudes, higher beam resting EEG power in the 0-5 Hz. frequency range, and higher number of EEG movement artifacts than did the worst-response group (Figure 3). The auditory evoked cortical response consisted of a complex wave form with an early positive peak (P_1) at 60 msec, followed by a negative peak (N_1) at 120 msec, a late positive peak (P_2) at 180 msec, and a late negative peak at 280 msec. When before-treatment auditory evoked responses were compared, it was found that the hyperkinetics who were later found to give the best clinical response had significantly higher evoked response amplitudes and lower recovery of evoked response amplitudes than did the hyperkinetics with the worst clinical response (Figure 4).

Eleven placebo treated hyperkinetic subjects were matched for age and IQ with the Ritalin treated groups to control for test-retest changes. On result following treatment, the placebo group and both good and poor Ritalin treatment groups showed a decrease in mean skin conductance but there were no significant between group differences (Figure 5). Following treatment both the placebo and poor clinical response to Ritalin groups had an increase in power in the resting EEG and in the amplitude of all three components of the auditory evoked response. The hyperkinetic children who obtained the best clinical response to Ritalin differed from both the placebo and the poor response to Ritalin group in that they had little or no increase in

[illegible] [illegible] in the resting EEG and their auditory evoked [illegible] were not increased but were decreased (Figure 5).

<u>[illegible]</u>: Hyperkinetic children who obtained a best clinical response to stimulant medication differed on several physiological measures from those who responded poorly. Before treatment the best responders had greater resting EEG mean amplitudes, greater resting EEG range of amplitudes, more slow wave activity (low frequency power), more movement artifacts and larger evoked cortical responses. The finding that Ritalin treatment is significantly better than placebo is consistent with previous studies on the efficacy of stimulants in this group of children[10,11]. The greater incidence of abnormal behavior in hyperkinetic children when compared with normal control subjects (Table 1) agrees with a report by Stewart et al[12].

Before-treatment low skin conductance level in the best-response group suggests low CNS arousal level. This interpretation follows from the generally accepted view that skin conductance level is an index of level of arousal[13]. The high amplitude of the auditory evoked response observed in the before-treatment studies of the best-response group also suggests low CNS arousal. This follows from reports that sensory evoked response amplitudes in human subjects tend to decrease with increased arousal produced by shock stimuli[14] or by stimulation of the mesencephalic reticular formation in one subject[15]. We also propose that the before-treatment high mean resting EEG amplitude, large range of resting EEG amplitude, and high energy in the low frequency band of the resting EEG suggest a low arousal type resting EEG in the best clinical response group.

Therefore, the skin conductance level, the resting EEG, and the evoked cortical response measures all suggest low CNS arousal before treatment in those children who benefit most from stimulant medication.

[illegible] Laboratory tests were the following week of Ritalin [illegible]. All subjects were given a single clinical therapeutic dose one [illegible] hours before the second laboratory test. The placebo group showed a large increase in power in the low frequencies of the resting EEG (slow wave activity) and an increase in evoked response amplitudes (Figure 5). These changes are consistent with lower CNS arousal[14, 19] and with the often reported observation that subjects are more relaxed and less tense the second time in the laboratory. In the Ritalin treated groups there are two opposing effects in operation: (1) the effect of the second time in the laboratory, noted above, which tends to produce lower arousal levels, and (2) the CNS stimulant effect of Ritalin, which tends to raise arousal levels. The best-response to Ritalin group had a decrease in evoked response amplitudes and little or no change in slow wave activity on their second test session. The worst-response group had a significant increase in slow wave activity and in evoked response amplitudes. These differences between the groups with the best and worst clinical response indicate more CNS arousal effect from Ritalin medication in the hyperkinetic patients who had the best clinical response. These results suggest that those patients with lowest arousal before treatment got the best clinical response to Ritalin, and their EEG and evoked response arousal indicators suggest that the CNS arousal effect of the Ritalin has been greatest. A previous study of 24 hyperkinetic children reported that most hyperkinetic children have abnormally low arousal states as determined by skin conductance level measures, while some have abnormally high arousal states[16]. It has also been suggested that those hyperkinetic children with low arousal may attempt

to [illegible] than that by [illegible] motor activity[16]. The larger number of [illegible] artifacts in the low arousal group reported here is consistent with that theory.

Drug studies of this disorder report two groups of patients, the good responders and poor responders. Millichap[17] has reviewed published results of drug studies as of November 1967. Percentage of improvement ranged from 83 percent for Ritalin to 21 percent for Prolixin. In all studies, however, there was a group who did not respond to drug treatment.

Our results suggest a fundamental physiological difference between the good and poor responders. One group is characterized by low CNS arousal and good clinical response to stimulant treatment, and another group is characterized by high CNS arousal and poor response to stimulant treatment.

Follow-up studies[12,18,19,20,21] of the Hyperkinetic Child Syndrome indicate that there is a group who develop serious antisocial behavior in adolescence and adulthood and the Menkes study[18] indicates that there is a group who develop psychosis in later life. Family studies[22,23] indicate that the fathers of hyperkinetic children exhibit a high degree of sociopathy and alcoholism, while their mothers exhibit a high degree of hysteria and (to a lesser extent) alcoholism. There is some indication[19,24,25] that it is the hyperkinetic children who come from families with alcoholism and mental illness who do not respond to stimulant treatment and who become antisocial adolescents and adults.

It is interesting to speculate that the group with high arousal and poor response to stimulant treatment in our study may be the ones who come from pathological families and who will become antisocial in later life.

the correlation between psychological families, the hyperkinetic child syndrome, and later life delinquent behavior can be taken as evidence for either an environmental or genetic biological factor in the development of these disorders. Our results would be more consistent with genetic factors playing a major role.

This is a report of the first year of a three-year study. Due to the small number of subjects in the groups described here, the significance of the results reported will depend upon future research. We plan to continue the laboratory studies and intensively study the families of the poor responders and the good responders and to follow both groups over a period of years to further clarify the relationship between these physiological, hereditary, and environmental factors.

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FIGURES

FIGURE 1

Comparison of hyperkinetic children and normal controls.

FIGURE 2

Comparison of the six hyperkinetic subjects with the best clinical response to Ritalin treatment with the five hyperkinetic subjects with the worst clinical response.

FIGURE 3

Comparison of normal controls and the hyperkinetics with the best and the worst clinical response to Ritalin on pre-treatment laboratory measures.

FIGURE 4

Comparison of normal controls and the hyperkinetics with the best and the worst clinical response to Ritalin on pre-treatment auditory evoked responses at slow stimulus (1 stimulus per 2.5 seconds) rate.

FIGURE 5

Comparison of best response, worst response and placebo groups on change in laboratory measures on second laboratory session and following Ritalin treatment. Arrows indicate direction of change. Evoked response amplitudes are group mean changes in microvolts.

TABLE 1

Attributes which differed at $p < .001$ level between hyperkinetic children and normal controls.

	N	AGE		WISC	
		$\bar{X}$	RANGE	$\bar{X}$	SD
HYPER	32	7yr - 9mo	6 - 9 yrs	104	12.3
CONTROL	21	7yr - 9mo	6 - 9 yrs	110	13.4

FIGURE 1

BEH. RESP.	N	MEAN AGE	MEAN I.Q.	TEACH. RATING X SCORE	TEACH. RATING X % IMPROV.
BEST	6	7 yr. - 4 mo.	105	59	71****
WORST	5	7 yr. - 9 mo.	107	46	16
CONTROL	11	7 yr. - 7 mo.	108	15	DOES NOT APPLY

**** P < .001

FIGURE 2

Clinical Response to Ritalin	Mean Skin Conductance Level in (mho)	E.E.G. Background			Number of E.E.G. Movement Artifacts
		Amplitude		Mean Power 0-8 Hz	
		Mean (μV)	Mean Range (μV)		
Best N=6	16.1	16.4*	110*	255**	304**
Worst N=5	24.4	13.2	87	216	163
Control N=11	20.0	15.3	104	188	208

Statistical comparision is between best and worst groups only

* $p < .05$

** $p < .01$

Mann-Whitney U

FIG. 3

Clinical Response	Auditory Evoked Response		
	Peak to Peak Mean Amplitude (P_2-N_2) at Slow Rate (2/s)	Percent Recovery	
		$P_1 - N_1$	$N_1 - P_2$
Best N=6	19.9 *	27 *	16 **
Worst N=5	10.9	92	108
Controls N=11	21.9	—	43

Statistical comparison is between Best and Worst groups only.
Mann-Whitney U

* $p < .05$

** $p < .02$

Fig. 4

Clinical Response to Ritalin	Mean Skin Conductance in mmho	Power 0-8 Hz Mean Percent change	Auditory Evoked Response Peak to Peak Amplitudes Mean change in MV		
			P_2 -- N_2	N_1 -- P_2	P_2 -- $N_{2'}$
Placebo	↓ 4.5	↑ 50	↑ 1.5	↑ 2.9	↑ 5.6
Best	↓ 4.3	↑ .09 *	↓ 1.4 **	↓ 2.1 **	↓ 4.8
Worst	↓ 14.6	↑ 25.0	↑ 4.8	↑ 5.5	↑ 1.7

Statistical Comparison is Between Best and Worst Groups Only

Mann-Whitney U

* $p < .05$

** $p < .01$

Fig. 5

TABLE 1

Percentage of Behaviors Found in
Hyperkinetic Boys and in Normal Boys
Matched for Age and I.Q.

Behaviors	HK's	Normals
Fighting with peers	93	7
Unable to take correction	86	0
Rocking, leg jiggling	86	14
Dances, wiggles hands	86	14
Unusually active	86	14
Unable to sit through school period	86	21
Unable to follow directions	79	7
Difficult to get to bed	79	7
Poor relationships with peers	71	0
Temper tantrums	71	7
Does not complete projects	71	7
Hard to get to sleep	71	7
Wakes early	71	7
Defiant	71	14
Unable to sit through meal	64	0
Leaves doctor's office	64	14

$p < .001$